TABLE 5

Baseline Characteristics of Subjects Who Completed the 3-Month Monotherapy Phase of the Trial

	Metformin Group (n = 15)	Troglitazone Group (n = 13)	p =
Age (years)	51 (±3)	53 (±2)	0.32 (NS)
Weight (kg)	99 (±4)	96 (±7)	0.68 (NS)
BMI (kg/m^2)	33.7 (±1.8)	34.0 (±2.3)	0.94 (NS)
FPG (after "wash-out")	287 (±22)	275 (±21)	0.71 (NS)
HbA_{1c} (at screening)	9.8 (±0.5)	9.3 (±0.5)	0.42 (NS)
Fasting insulin	24 (±3)	35 (±7)	0.16 (NS)
Fasting C-peptide	1.9 (±0.1)	2.3 (±0.2)	0.13 (NS)

The patients were evenly matched for age, body mass index (BMI), fasting plasma glucose (FPG), HbA_{1c}, and fasting insulin and C-peptide. The treatment group was in general obese, moderately diabetic, and had a mean BMI of 33.5 kg/m^2, a mean HbA_{1c} (prior to starting the study) of 9.6%, and a mean FPG of 280 mg/dL.

After the initial 3-month period of monotherapy, the remaining subjects were dosed with a combination of metformin and troglitazone (1000 mg metformin BID, 400 mg troglitazone QD) for an additional 3-month period.

At 3 months on monotherapy, both metformin and troglitazone caused a 20% decrease from baseline of FPG; 58 mg/dL and 54 mgldL, respectively (FIG. **8**). HbA_{1c} levels did not change significantly with either drug. Mean post-prandial glucose decreased about 25% for both groups (metformin 87 mg/dL, troglitazone 83 mg/dL), as shown in FIG. **9**. Post-prandial circulating insulin and C-peptide decreases were insignificantly different from baseline for both treatment groups. Following a 12-hour fasting period, all subjects were given a hyperinsulinemic-englycemic clamp assay. After the 3-month monotherapy treatment, EGP decreased from 108 to 87 mg/m^2/min (18%) in the metformintreated group (FIG. **10**A), while troglitazone had no effect on EGP (FIG. **10**B). In contrast, metformin caused less than 27% increase in glucose disposal rate (GDP) (240 to 272 mg/m^2/min) (FIG. **10**B), whereas troglitazone caused a 97% increase (172 to 265 mg/m^2/min) (FIG. **10**B).

When the study patients were given the combination of metformin and troglitazone for 3 months, dramatic and unexpected effects were observed. Fasting plasma glucose levels decreased an additional 18% (41 mg/dL) as shown in FIG. **8**. Compared to baseline values, the mean decrease in FPG in all subjects over the entire 6-month treatment period was 98 mg/dL, or 35%. During the meal tolerance test, combination therapy caused an additional 21% decrease in plasma glucose (PG), or 54 mg/dL (FIG. **11**). During the entire 6-month treatment period, total PG fell 41% or 140 mg/dL. HbA_{1c} levels decreased 1.2% during the combination therapy (FIG. **12**).

The foregoing study establishes that the combination of metformin and troglitazone causes a clinically significant and unexpected further lowering of both fasting and post-prandial glucose compared to either agent used alone. The combination provided by this invention thus provides further improvement in glucose control, without stimulation of insulin secretion.

Even more surprising are the clinical results observed when using a three-way combination of biguanide, sulfonylurea, and glitazone. A clinical trial was carried out assessing the effects of metformin, glyburide, and troglitazone when compared to a typical treatment regimen of glyburide and metformin. Two hundred NIDDM patients were enrolled in a double-blind, randomized, placebo-controlled multicenter study. All enrolled patients had compromised glycemic control and were currently treated with a sulfonylurea (comparable in dosage to at least 20 mg of glyburide) and at least 1500 mg of metformin daily. Of the 200 patients enrolled, 178 completed the 24-week trial. The study population consisted of 57% males, 43% females, with median age of 59. Patients had an average duration of NIDDM of 11.3 years. The population had an average weight of 85 kg (187 lbs), and BMI of 30.1 kg/m^2. At the start of the trial, 101 patients received oral dosing of troglitazone (400 mg once daily), a sulfonylurea (SU), and metformin. The control group of 99 subjects received a sulfonylurea and metformin. The primary efficacy parameter measured was HbA_{1c}. Secondary efficacy parameters were FSG, C-peptide, serum total insulin, BMI weight, triglycerides, total cholesterol (TC), high-density lipoprotein (HDL), and low-density lipoprotein (LDL). Baseline glycemic levels at the start of the trial were: HbA_{1c}: 9.7%; FPG: 234 mg/dL; circulating insulin level: 14.4 μIN/mL; C-peptide: 3.4 ng/mL. The results of the clinical study after 24 weeks of treatment are presented in Table 6.

TABLE 6

Changes From Baseline at 24 Weeks

	SU + Metformin	SU + Metformin + Troglitazone	Adjusted Difference
HbA_{1c}	+0.1	−1.3 (p < 0.001)	−1.4
FPG	+6	−42 (p < 0.001)	−48
Circulating Insulin	+1.4	−2.8 (p < 0.001)	−3.3
C-peptide	0	−0.2 (p = 0.16)	−0.2
Triglycerides	+43	−36 (p = 0.07)	−67
Total Colesterol	+6	+8 (p = 0.05)	4.8
HDL	+1	+4 (p = 0.01)	3
LDL	+2	+11 (p = 0.002)	9

In the foregoing study, plasma glucose levels were reduced by 42 mg/dL at Week 8 in the group receiving the triple combination. This is a dramatically rapid reduction in FPG, showing the unexpectedly fast onset of action achieved with the triple combination, and the synergy associated with metformin, sulfonylurea, and glitazone. This represents good glycemic control in about one-half the time period normally observed in clinical settings using antidiabetic agents in monotherapy, or even using a combination of sulfonylurea and biguanide. Equally surprising was the dramatic reduction in endogenous insulin (19%) caused by the triple combination. Moreover, while the sulfonylurea/metformin combination had no effect on C-peptide levels, the triple combination of sulfonylurea/biguanide/glitazone caused a 7% reduction. Similarly, while the sulfonylurea/metformin treated group had an increase in triglycerides of 43 mg/dL, the sulfonylurea/glitazoneibiguanide combination caused a reduction of 36 mg/dL.

The foregoing clinical trial establishes that three-way combinations of sulfonylurea/biguanide/glitazone are surprisingly effective at reducing HbA_{1c}, and cause a very rapid and significant reduction in plasma glucose levels. Such combinations are especially well-suited to rapidly bringing under control a patient suffering from NIDDM and having dangerously high levels of plasma glucose. Another important and significant aspect of the foregoing clinical trial is the fact that the patients experienced very few adverse events, and the dropout rate was extremely low.

What is claimed is:

1. A composition comprising from about 3 mg to about 250 mg of a sulfonylurea antidiabetic agent, from about 5 mg to about 2500 mg of a glitazone antidiabetic agent